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Paraneoplastic Syndromes in Lung Cancer

Dilaver Tas

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Abstract

In recent years, the incidence of lung cancer (LC) has been increasing throughout the world and is the most common type of cancer in all regions of the world, occurring more frequently in men than in women. Paraneoplastic syndromes (PNS) refer to clinical conditions that develop in relation to tumors, without physical effects of the primary or metastatic tumors. The development of PNS is not associated with the size of the primary tumor or the extent of metastases. It is usually seen in small-cell lung cancer (SCLC) as well as other types of lung cancer. PNS developed in almost 1 in 10 patients with lung cancer and it may be an indicator for the diagnosis of lung cancer and it can be seen during later stages of cancer or at the time of cancer recurrence. Accordingly, the identification of these syndromes can be helpful in the early diagnosis of occult cancers, allowing timely treatment. PNS decreases the quality of life of the patients with cancer and thus requires specific treatment. Moreover, these conditions can be used as a marker of cancer activity and can predict prognosis. In this section, a detailed description of PNS is provided.

Keywords: lung cancer, small-cell lung cancer, non-small-cell lung cancer, paraneoplastic syndromes

1. Introduction

1.1. Definition

The term “paraneoplastic syndrome (PNS)” refers to tumor-related symptoms and findings that are independent of the direct, local extent or physical effects of metastases. PNS develops in response to the effects of hormones and cytokines released from cancer cells, or due to the immunologic response of cancer cells [1, 2]. In this regard, there is no single mechanism

underlying the development of PNS, and potential mechanisms have not yet been clearly understood. On the other hand, several tumor-secreted proteins that may be associated with the development of PNS have been defined in the recent years. Generally, the ectopic production of peptide hormones with hormonal activity and immunological mechanisms can be seen in patients with PNS.

The diagnosis and treatment of PNS are complementary parts of lung cancer (LC) management. PNS may involve several organs and systems, and so may therefore result in neurological, dermatological, hematological, nephrological, rheumatologic, metabolic, immunologic and constitutional signs and symptoms.

1.2. History

In 1865, Armand Trousseau, a French internal diseases specialist, stated that the identification of unexpected or migratory thrombophlebitis could indicate an occult visceral malignancy [3], and today, the development of superficial migratory thrombophlebitis related to visceral cancer is known as Trousseau syndrome. An Austrian dermatologist, Ferdinand von Hebra, underlined the significance of internal disease in the etiology of several skin manifestations such as urticaria, generalized pruritus, xanthoma, and pemphigus. In 1868, he further stated that skin pigmentation could be an indicator of cervical cancer [4, 5]. In 1890, a French physician named Auché defined peripheral nervous system involvement in patients with stomach, pancreas, and uterus cancer [6], while acanthosis nigricans associated with malignancy was reported separately by Pollitzer and Janovsky in 1890 [7]. Later, Brown identified the Cushing syndrome in a patient with small-cell lung cancer (SCLC) in 1928 [8], and in 1933, neuropathy development was reported in a patient with oat cell carcinoma (small-cell lung cancer) [9]. Guichard and Vignon used the term “paraneoplastic” for the first time in 1949 when they identified central and peripheral neuropathies in a patient with cervical cancer [10]. In 1957, Schwartz et al. reported hyponatremia in a patient with LC [11]. In 1967, Bartter and Schwartz defined the syndrome of inappropriate antidiuretic hormone secretion (SIADH) [12]. The relationship between the neurological PNS and LC was first suggested by Oppenheim at the end of the nineteenth century [9].

In the following years, etiologic and pathogenetic studies were carried out to evaluate the relationship between PNS and cancer including LC. Additionally, new PNS definitions and new developments have been made which are still ongoing.

1.3. Epidemiology

LC is currently the most common type of cancer throughout the world [13]. Due to the high incidence rate of LC and the relatively high frequency of PNS in SCLC cases, LC-related PNS is more common than other types of cancer [14–17]. However, it is difficult to estimate PNS frequency due to challenges in the identification of PNS and uncertainty in the differentiation of its symptoms because of the underlying disease. PNS can be seen in all age groups of patients with cancer. However, due to the nature of cancer, it is more common in middle-aged and older individuals. PNS develops in 1–7.4% of all patients with cancer, although it is estimated to develop in 20% of all patients with cancer [14]. The inclusion of generalized malignancy symptoms, such as cachexia and fever, increases PNS frequency up to 70% [18].

PNS can occur both in patients with SCLC and with non-small-cell lung cancer (NSCLC). SCLC has a neuroendocrine origin and PNS is more common in such cancer types. PNS is seen by 7–15% of all patients with LC. Systemic symptoms and findings of PNS develop in 50% of patients with SCLC and almost 10% of patients with NSCLC [19]. PNS develops secondary to LC and increases the severity of the disease. It is therefore crucial to recognize PNS in these patients.

Incidences of PNS will increase in the coming years thanks to the improvements in diagnosis and treatment of LC as well as in the diagnosis of PNS.

1.4. Pathophysiology

PNS may develop under the effects of substances released by the tumor or as a result of the cross-reactions between tissues and the antibodies produced against the tumor.

Studies investigating the pathogenesis of PNS offer some evidences that PNS develops based on different pathogenetic mechanisms, such as:

1. The production of special substances by tumor cells, leading specifically to the development of PNS. These substances may be hormones, growth factors, vasoactive peptides, cytokines, enzymes or other signaling molecules.
2. Abnormal immune response of the host organ to the neo-antigens produced by the tumor or to other tumor products [7, 18, 20].

Endocrinologic PNS generally develops due to the increased production of hormones or hormone precursors by malignant cells. The best example for this is paraneoplastic Cushing syndrome seen in patients with SCLC [21].

Paraneoplastic hypercalcemia is an example of PNS associated with cytokine production. Some cytokines (IL-1, 3, and 6, prostaglandins, TGF- α , TNF- α [lymphotoxin], and TNF- β [cachectin], etc.) that are synthesized by the malignant cells may result in hypercalcemia by activating osteoclasts [22].

Cancer cells are recognized by the immune cells and lead to the production of antibodies. As cancer cells are identical to normal cells in nature, the antigens on the cancer cells are similar to those of normal cells. Therefore, the formed antibodies may have a cross-reaction with normal tissues. This pathophysiological condition is most commonly seen in neurological PNS [23, 24].

The main mechanism underlying above-described pathological response in patients with LC and other types of cancer still presents an unanswered question. The most appropriate answer to that would be inappropriate gene expression (IGE). IGE may be described as the formation of an inappropriate gene programmed to produce tumoral proteins in cancer cells. This may lead to the development of new disorders that will negatively affect patient well-being. Thus, the quality of life of the patient is impaired and the severity of the disease increases [18].

Genetic studies that will be performed in the future to identify IGEs in cancer patients will allow the early detection of PNS, even before the clinical diagnosis, and more importantly, will be helpful to identify malignant formations.

2. Paraneoplastic syndromes

The diagnosis of PNS is relatively challenging, as lesions may develop in regions distant to the cancer and may not resemble a cancer-related disease, and the disorder has benign forms in general as well as malignant forms. PNS should be suspected in the presence of below characteristics: absence of a defined etiology for the associated syndrome; correlation between the time of diagnosis of the syndrome and that of cancer; clinical and histological remission after complete surgical or chemotherapy treatment and a worsening of symptoms due to tumor residue [25].

Although PNS may be associated with a lot of malignancies, they are associated most commonly with lung cancer, specifically SCLC. Humoral hypercalcemia and SIADH, which is seen in orderly squamous cell and SCLC, are the most common PNSs. Multiple paraneoplastic syndromes can be seen in patients with SCLC. In the literature, there have been patients with two or more paraneoplastic syndromes associated with SCLC, even though rarity. Paraneoplastic syndromes usually have a course parallel to the underlying malignancy. Treating the underlying tumor is the first choice and symptomatic therapy can be useful [2, 26–29].

2.1. Classification

Paraneoplastic symptoms in LC can be seen almost in all systems, which can be listed as follows:

- Endocrine paraneoplastic syndromes
- Neurologic paraneoplastic syndromes
- Dermatologic paraneoplastic syndromes
- Rheumatologic paraneoplastic syndromes
- Nephrological paraneoplastic syndromes
- Hematologic paraneoplastic syndromes
- Others

2.2. Endocrine paraneoplastic syndromes

Endocrinological PNS generally develops due to excessive synthesis of hormones or hormone precursors with low bioactivity, or the conversion of the precursors to more effective product(s) in the tumor tissue.

2.2.1. Ectopic Cushing syndrome

Secretion of ectopic adrenocorticotrophic hormone (ACTH) from the tumor may result in Cushing syndrome, and high ACTH levels can be noted in almost 50% of patients with LC. Cushing syndrome may develop in 1–5% of patients with SCLC [30, 31], and of all the pulmonary

neuroendocrine tumors, about 1–2% are accompanied by Cushing syndrome due to ectopic ACTH secretion, or the production of its precursor, proopiomelanocortin (POMC) [32].

Patients are typically admitted to clinics due to myopathy, centripetal obesity, facial plethora, hypertension, osteoporosis, hyperglycemia, hirsutism, and acne. The clinical symptoms have a rapid onset and are generally accompanied by hypokalemia and hyperglycemia.

Due to its rapid onset, patients generally are found to have electrolyte imbalances rather than having a cushingoid appearance, although typical cushingoid characteristics such as moon face and buffalo hump generally do not manifest, as hypercortisolism is an acute phenomenon and patients do not live long enough for the manifestation of morphological changes [33, 34].

Increased levels of free cortisol in the urine, elevated serum levels of ACTH or ACTH precursors, hypokalemia and hyperglycemia are helpful for the diagnosis of ectopic Cushing syndrome (ECS).

The prognosis of SCLC patients with Cushing syndrome is worse than in SCLC patients without Cushing syndrome [35].

Treatment essentially involves treating the primary tumor. In the presence of non-resectable tumors, medications that inhibit steroid biosynthesis (metyrapone, ketoconazole) can be used for the treatment of ECS. Aminoglutethimide can be used to prevent androgenic side effects and octreotide may be helpful in reducing ACTH release. A bilateral adrenalectomy may also be considered [31].

2.2.2. Inappropriate antidiuretic hormone syndrome

Inappropriate antidiuretic hormone syndrome (IADHS) develops as a result of free water retention and increased extracellular fluid volume due to the irregular release of the antidiuretic hormone (ADH). This initiates a process characterized by a progressive dilution of plasma sodium and sodium loss through the kidneys.

It is generally seen in patients with SCLC, accounts for around 75% of all cancer-related IADHS. It is seen in 7–16% of patients with SCLC but may also occur in patients with NSCLC [36, 37].

Antidiuretic hormone (ADH) levels are generally elevated in LC patients with IADHS and in addition, patients may also have increased levels of atrial natriuretic peptide [38].

IADHS symptoms rarely manifest when plasma sodium levels are higher than 125 mEq/L. Plasma sodium levels below 125 mEq/L may result in symptoms such as weakness, tiredness, nausea, headache, lethargy, and confusion, while levels below 120 mEq/L may lead to seizure and coma [39].

Based on the definition of Bartter and Schwartz, a diagnosis of IADHS can be made in the presence of following findings:

- Serum Na < 134 mEq/l
- Plasma osmolality <275 mOsm/kg

- Urine osmolality >500 mOsm/kg
- High urinary sodium concentration (>20mEq/l)
- Absence of clinical signs of volume depletion
- Presence of normal adrenal functions
- Presence of normal thyroid functions [1, 12]
- Presence of IADHS is a marker of poor prognosis [38]

If plasma sodium levels are higher than 130 mEq/L, fluid intake may be limited (500 mL/day) and/or patients may be given demeclocycline, which is a medication that blocks the response of renal tubules to ADH. A slow infusion of hypertonic saline solution and an IV furosemide infusion may be preferred in severe cases [31].

2.2.3. Hypercalcemia

Hypercalcemia develops in 6% of LC patients, and is most commonly seen in the presence of squamous cell carcinoma [40, 41]. In LC, hypercalcemia is caused by the production of parathyroid hormone-related protein (PTHrP) of the tumor and secretion of parathyroid hormone. Another mechanism leading to the development of hypercalcemia involves PTHrP increase as a result of granulocyte colony-stimulating factor signal. While increased $1.25(\text{OH})_2$ Vitamin D synthesis may result in hypercalcemia in some malignancies, this mechanism is not associated with hypercalcemia in LC [41].

Early symptoms of hypercalcemia include loss of appetite, nausea, vomiting, constipation, numbness, polyurea, polydipsia, and dehydration, while late symptoms include renal failure, nephrocalcinosis, confusion, and coma.

Elevated serum levels of ionized calcium, normal or decreased levels of parathyroid hormone and high PTHrP levels are diagnostic factors [9].

Treatment is essentially based on the treatment of the tumor-causing hypercalcemia. Symptomatic patients with high serum calcium levels should be treated with hydration and bisphosphonates, and any calcium supplements, thiazide diuretics, and lithium, all of which may alleviate hypercalcemia, should be discontinued [42].

2.2.4. Other endocrine paraneoplastic syndromes

In LC patients, hypoglycemia may occur due to ectopic insulin secretion and insulin-like growth factor (IGF) secretion.

Acromegaly may also occur as a result of ectopic growth hormone-releasing hormone (GHRH) or IGF secretion.

Moreover, carcinoid syndrome may develop in relation to the secretion of serotonin and similar vasoactive amines [41, 43].

2.3. Neurologic paraneoplastic syndromes

Neurologic PNS may develop by the involvement of central nervous system, peripheral nervous system or the neuromuscular junction and muscles. The majority of patients with neurologic PNS have SCLC (at a rate of 5%). In its pathogenesis, immune-system mediated reactions are seen in general. Immune cross-reactivity is seen between tumor cells and components of the nervous system [9, 29, 44].

International criteria have been determined to facilitate the diagnosis of paraneoplastic neurologic syndromes, defining “definite” and “possible” diagnoses. The definite diagnostic criteria are as follows:

- neurological symptoms that will develop cancer within 5 years and commonly accompanying with cancer (limbic encephalitis, cerebellar degenerations, etc.);
- nonclassical neurologic syndrome that improves after cancer treatment without concomitant immunotherapy;
- nonclassical neurologic syndrome with positive antibodies and a diagnosis of cancer within 5 years; and
- neurologic syndromes accompanied by “well-characterized” antibodies in the absence of a cancer diagnosis (anti-Hu, anti-CV2, anti-Ri, anti-Yo, anti-Tr, and anti-Ma2).

There are three categories of possible paraneoplastic neurologic syndrome diagnoses:

- presence of classical neurologic syndrome in the absence of cancer or antibodies, but a high risk of underlying tumor;
- presence of neurologic syndrome with non-classical antibodies in the absence of cancer; and
- presence of classical neurologic syndrome without antibodies or a malignancy [9, 45].

2.3.1. Encephalomyelitis

Paraneoplastic encephalomyelitis should be considered in the presence of neuronal loss and inflammation in multiple regions of the central nervous system, primarily in the hippocampus (limbic encephalitis), Purkinje cells of the cerebellum (cerebellar degeneration), brainstem (brainstem encephalitis) and medulla spinalis (myelitis). Dorsal root-ganglion (sensorial neuropathy), as well as sympathetic and parasympathetic nerve and ganglions (orthostatic hypotension, gastrointestinal paresis, arrhythmia, erectile dysfunction) are known to be involved in the majority of the cases [46, 47].

It is thought to be developed with SCLC and due to the immune response that develops against the neural proteins expressed by the tumor. The most commonly identified antibody in paraneoplastic encephalomyelitis is the Hu (ANNA-1) antibody, although cases associated with CV2, amphiphysin, and Ri antibodies have also been reported.

While it may start with relatively milder and focal signs such as *epilepsia partialis continua*, nonconvulsive epileptic status or frontal-type ataxia, the findings rapidly progress within weeks or months and may result in death in general. Neurological outcomes may not be satisfying despite the treatment, as irreversible neuronal damage occurs in most of cases when the diagnosis is made. The worst neurological outcomes are seen in paraneoplastic encephalomyelitis accompanied by Anti-Hu antibodies [48].

In addition to cancer treatment, immunomodulation plays a key role in the treatment of encephalomyelitis, and corticosteroids, steroid-sparing agents (azathioprine, cyclophosphamide, etc.), rituximab, IVIG, and plasmapheresis can be used for treatment [44].

2.3.2. *Limbic encephalitis*

Paraneoplastic limbic encephalitis manifests with major findings such as short-term memory loss, behavior/mood changes and epileptic seizures, and confusion, irritability, depression, sleep problems, hallucinations and psychosis in addition to major findings [49]. Moreover, hyperthermia and endocrine disorders may also develop due to hypothalamic dysfunction. Antibodies produced against the Hu, Ma2, CV2 and amphiphysin antigens expressed by the tumor have been identified in patients with paraneoplastic limbic encephalitis. For the diagnosis, demonstration of epileptic activity in the electroencephalographic examination, demonstration of temporal lobe involvement in magnetic resonance imaging (MR2), and an investigation of the cerebrospinal fluid (CSF) and auto-antibody test are required. The neurologic response to treatment varies between patients with paraneoplastic limbic encephalitis, while 30–50% of patients may recover after the tumor treatment.

Just like in encephalomyelitis, immunomodulation plays a key role in treatment along with cancer-specific therapies, and corticosteroids, steroid-sparing agents (azathioprine, cyclophosphamide, etc.), rituximab, IVIG, and plasmapheresis can be used for treatment [44].

2.3.3. *Cerebellar degeneration*

Paraneoplastic cerebellar degeneration is one of the most common PNS. Depending on the widespread cerebellar Purkinje cell death, it may have an acute or subacute onset and courses with a rapidly progressing pancerebellar syndrome. The antibodies associated with cerebellar degeneration include anti-Yo, Tr, Hu, Ma2, and Ri [50]. However, the most well-defined and frequently seen paraneoplastic cerebellar degeneration is associated with the Yo antibodies. Before developing findings of neurologic deficit, patients may experience flu-like prodromal signs and may then develop an ataxic gait, dysarthria, dysphagia, diplopia, blurred vision, and transient opsoclonus. Patients initially have normal MR and CSF findings, however, inflammatory findings in CSF develop rapidly and an MR may demonstrate advanced cerebellar atrophy. Fast and effective treatment may prevent the progression of symptoms, but cerebellar degeneration is one of the most treatment-resistant PNS.

Like in limbic encephalitis, treatment may include the use of corticosteroids, steroid-sparing agents (azathioprine, cyclophosphamide, etc.), rituximab, IVIG, and plasmapheresis [44].

2.3.4. *Lambert-Eaton myasthenic syndrome*

Almost 60% of the Lambert-Eaton myasthenic syndrome (LEMS) cases have a paraneoplastic origin. SCLC is observed in the vast majority of cancer cases with LEMS, while other types of cancer are seen in a small number of cases [51]. LEMS develops in 3% of all SCLC cases, and LEMS develops as a result of the autoimmune response to the P/Q-type anti-voltage-gated calcium channels (VGCC) that exist on the pre-synaptic membrane of the neuromuscular junction, and 95% of the cases are found to be positive for this antibody. Of all cases with LEMS and SCLC, 64% are positive for SOX1 antibodies [41], and patients are generally admitted with proximal muscle weakness, reduced or absent deep tendon reflexes, and findings of autonomic function impairment. Tumor treatment is known to be a key factor to predict the neurological outcomes. In cases with SCLC, treatment 3,4-diaminopyridine, a potassium channel antagonist, may provide significant recovery, and azathioprine and prednisolone may also be used for the treatment [41, 51, 52].

2.3.5. *Opsoclonus-myoclonus*

This syndrome is associated with involuntary chaotic conjugated rapid eye movements and myoclonic discharges in the head, neck, face, trunk, and legs as well as potential cerebellar ataxia. In some adult cases, anti-Ri, anti-Hu, anti-amphiphysin, and P/Q-type VGCC antibodies may accompany cancer. Paraneoplastic opsoclonus and myoclonus respond well to treatment. Successful treatment can be achieved by the resection of the underlying tumor and elimination of circulating antibodies such as corticosteroids, intravenous immunoglobulin and plasmapheresis [41, 53].

2.3.6. *Chronic gastrointestinal pseudo-obstruction*

Chronic gastrointestinal pseudo-obstruction (CGP) is an autonomic neuropathy that is characterized by gastrointestinal dysmotility without a mechanical obstruction, leading to symptoms of abdominal pain, nausea and constipation [41].

While CGP generally occurs in patients with SCLC, it may also be noted in patients with NSCLC. Anti-Hu antibodies are frequently positive. In addition to cancer treatment, agent such as octreotide, prednisone, and azathioprine can be used for the treatment of CGP [41, 54].

2.3.7. *Others*

Neurological PNS has a variety of clinical manifestations. Other than above-described syndromes, patients may experience subacute sensory neuropathy involving the peripheral nervous system, acute sensory-motor neuropathy (Guillain-Barre Syndrome, brachial neuritis),

neuropathy with vasculitis, myasthenia gravis involving the neuromuscular junction and muscles, acquired myotonia, and acute necrotizing myopathy [41].

2.4. Dermatologic paraneoplastic syndromes

Dermatologic paraneoplastic syndromes are generally seen before patients are diagnosed with cancer. It is not possible to differentiate them from their benign variants in terms of clinical appearance and histopathological findings, although dermatologic PNS that suddenly develop at an atypical localization during the late stages of life and progress rapidly may indicate an accompanying malignancy and it should be investigated [7, 9, 17, 55].

2.4.1. *Acanthosis nigricans*

Acanthosis nigricans are characterized by skin hyperpigmentation and hyperkeratosis. It is most frequently seen on skin folds such as the axilla, neck, and groins. It usually accompanies lung adenocarcinoma.

The pathogenesis of acanthosis nigricans has not been clarified yet, although one possible etiology is the interactions between increased levels of insulin with insulin-like growth factor receptors and their effect on keratinocytes and dermal fibroblasts [56].

Malignant acanthosis nigricans regresses with the treatment of underlying malignancies, and isotretinoin may be preferred in cases that fail to recover [57].

2.4.2. *Polymyositis/dermatomyositis*

Polymyositis/dermatomyositis (PM/DM) is a disease characterized by specific skin findings (skin rashes and heliotropic appearance) and inflammatory myopathy accompanying with proximal muscle weakness. Violet-colored edema in periorbital tissues and the eyelids (heliotrophy), periungual telangiectasia, dystrophic changes in the cuticula and macular, violet-colored erythema on the forehead, neck, upper trunk, back, deltoid region, and dorsum of the hand are specific findings of PM/DM [58].

In 15–30% cases of PM/DM, an underlying malignancy is the cause of PNS. Ovarian and breast cancer in women and lung cancer in men are the most common malignancies associated with dermatomyositis [59].

Up to 30% of patients with PM/DM have auto-antibodies against cytoplasmic and nuclear antigens [60].

The treatment of the underlying malignancies can help in the resolution of the findings. Glucocorticoids are the most important medication for the PM/DM treatment, and immunosuppressive agents (azathioprine, cyclophosphamide, etc.) can also be beneficial [44].

LC patients with PM/DM have poor prognosis [61].

2.4.3. *Erythema gyratum repens*

Erythema gyratum repens (EGR) refers to multiple, erythematous, serpiginous, concentric-shaped lesions that can grow by almost 1 cm/day [62, 63], but no face, hand or foot involvement is observed.

Rather than benign pathological diseases, EGR generally appears in the presence of malignant diseases and a carcinoma can be detected in more than 80% of patients with EGR. The most common type of malignancy associated with EGR is a SCLC [7, 18].

The pathogenesis of the disease is unknown and its treatment is based primarily on the identification and treatment of the underlying malignancy.

2.4.4. *Erythema annulare centrifugum*

Erythema annulare centrifugum (EAC) is an eruption characterized by slowly progressing, annular or polycyclic erythematous lesions.

EAC, caused by benign reasons, is thought to develop due to hypersensitivity reaction. The pathogenesis of a figured erythema developing due to cancer, and thus EAC, is not clearly known, but a suggested hypothesis is that the tumor causes chemical changes in the surrounding tissues, inducing an antigenic status in these tissues, and these antigens lead to inflammation on the skin by causing cross-reactions since they are similar to the skin proteins [63].

EAC regresses with the treatment of the underlying tumor.

2.4.5. *Bazex syndrome (acrokeratosis paraneoplastica)*

Bazex syndrome is characterized by hyperkeratosis of the acral regions. It appears as erythematous, papulosquamous plaques on the nose and ears, and less frequently on the fingernails, hands, feet, knees, and elbows. The lesions are generally likened to psoriasis [64, 65]. Benign forms are less frequent than malignant PNS forms.

Its mechanism of development is still unclear, however, it regresses with tumor treatment. Like in most PNS cases, it may appear during LC recurrence.

2.4.6. *Tripe palms*

It is also known as palmoplantar keratoderma, pachydermatoglyphy, or palmar hyperkeratosis, and is generally seen with LC and 90% of the cases are associated with neoplasm. The most common types of tumors are lung and gastric cancers [41].

2.4.7. *Others*

Other cutaneous PNS seen in LC patients include paraneoplastic pemphigus, leukocytoclastic vasculitis, multicentric reticulohistiocytosis, sign of Leser-Trelat, pruritus, and finger clubbing.

2.5. Rheumatologic paraneoplastic syndromes

2.5.1. Hypertrophic osteoarthropathy

Hypertrophic osteoarthropathy (HO) is a syndrome characterized by finger clubbing and periostitis. Secondary HO, which is a PNS, is most frequently seen in LC, particularly in NSCLC [66]. It manifests with a clubbing of the fingers and toes, periostitis of the long bones and polyarthritis in some cases [67].

More than 70% of HO cases are associated with LC, and the incidence rate of HO among LC patients has been found to be 0.7% [41]. Periostitis is a well-known radiographic feature with a generally symmetric distribution, and periosteal reactions involving the long bones are present [67].

While theories have been suggested to explain the mechanisms of HO development, it is still unclear.

In addition to the cancer treatment, nonsteroidal anti-inflammatory drugs, bisphosphonates, and octreotide have been shown to be beneficial for the treatment of HO [41].

2.6. Hematologic paraneoplastic syndromes

Hematologic abnormalities such as anemia, leucocytosis, thrombocytosis, and eosinophilia are common in LC patients. However, not all of these are associated with a PNS. These conditions generally follow an asymptomatic course, and coagulopathies, granulocytosis, anemia, and thrombocytosis can be listed among hematologic PNS [9, 68].

2.6.1. Paraneoplastic coagulopathies

Patients with LC tend to develop thrombosis. Thrombotic risk in lung cancer patients is 20-fold higher than in the general population. Also the risk of thrombosis development in LC is higher than other types of cancer. Several studies have demonstrated that the incidence of cancer diagnosis increases during the first 6 months following venous thromboembolism and venous thrombosis. There are several mechanisms of coagulopathies in patients with LC. The main mechanisms include thrombocytosis, activation of clotting due to injury on the vascular walls, increase in the level and activation of clotting factors, and production of procoagulant factor secondary to tumor hypoxia [18, 29, 69].

Venous thrombosis and hypercoagulability are known as Trousseau syndrome, and while these are mobile in character, long-term anticoagulant treatment should be considered when they are detected.

2.6.2. Paraneoplastic granulocytosis

Granulocytosis, in the absence of infection or leukemia, is relatively common at the time of diagnosis or during the follow-up of patients with LC, and it is seen in 14.5% of patients with LC, and the majority of which are giant-cell lung carcinoma cases [2, 68, 70].

Granulocytosis develops due to the production of paraneoplastic hematopoietic growth factors and certain cytokines (IL-6) [70].

No specific treatment is required other than cancer treatment.

2.6.3. Paraneoplastic anemia

Anemia is seen in several types of cancer. It occurs as a PNS in cancer patients and is a normocytic normochromic anemia. This condition presents with low serum iron levels, normal or elevated ferritin level, normal iron stores, and low serum erythropoietin levels [2].

In LC, anemia as a PNS may also develop depending on autoimmunity, known as autoimmune hemolytic anemia, although antibodies with a specific association are unknown [71].

Anemia generally recovers after the cancer treatment, but patients may be given an erythrocyte suspension in cases of severe anemia.

2.6.4. Paraneoplastic thrombocytosis

Thrombocytosis frequency is 13–32% in LC patients. IL-6 is the cytokine that is known to play a role in the development of paraneoplastic thrombocytosis [41]. It requires no specific treatment.

2.7. Nephrological paraneoplastic syndromes

Nephrological PNS involves a group of disorders that develop as a result of glomerulopathy, which may cause electrolyte imbalance and urea-creatinine elevation, leading eventually to renal failure.

2.7.1. Membranous nephropathy

Membranous nephropathy, developing as a PNS, is most commonly seen in patients with LC, and primarily in patients with NSCLC [72]. Proteinuria leads to the development of hypoalbuminemia, resulting in edema in different parts of the body, and acute renal failure and hypertension may also develop in nephrotic syndrome.

The pathophysiology of membranous nephropathy involves the immune response given by tumor-related antigens, and antigen deposits in renal glomeruli have been reported in some patients [25, 73].

2.7.2. Others

Paraneoplastic glomerulopathies seen in LC patients include minimal change disease, IgA nephropathy, focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, crescentic glomerulonephritis, and thrombotic microangiopathies [73].

Effective cancer treatment will be sufficient when paraneoplastic glomerulopathies including membranous nephropathy are detected. However, renal functions should still be monitored and appropriately managed [74].

2.8. Ophthalmologic paraneoplastic syndromes

Ophthalmologic PNS related to the retina or optic nerves can be seen in LC cases, and particularly in SCLC, and retinopathy and optic neuropathy may develop and result in visual dysfunctions. Paraneoplastic syndrome in these cases is caused by the development of immune reaction. The antigens associated with paraneoplastic retinopathy are recoverin and alpha-enolase, whereas collapsin response mediator protein 5 is the antigen associated with paraneoplastic optic neuropathy [75].

Treatment is based primarily on immunosuppressive therapies. However, visual functions may not improve despite immunosuppressive therapy and effective treatment of underlying cancer [76].

2.9. Others

2.9.1. Cachexia

Cachexia is frequently seen in LC patients, and develops as a result of a rather complex process. Roughly, cachexia develops due to the chronic course of systemic inflammation associated with anorexia as well as the loss of muscle and fat mass in cancer patients [77]. While there is no specific treatment for cachexia, the most appropriate approach is to focus on cancer treatment and to provide nutritional support.

2.9.2. Fever

The diagnosis of fever as a PNS is difficult. Several conditions may cause fever in LC patients, including infections (bacterial, viral, parasitic, etc.), drug-induced fever, and autoimmune conditions other than cancer (rheumatoid arthritis, vasculitis, etc.). While the etiology of paraneoplastic fever is not completely understood, it is believed to be mediated by cytokines [78].

In addition to LC treatment, antipyretic medications can be preferred for the treatment.

3. Conclusion

Over the last century, there has been a great deal of progress in the diagnosis and pathogenesis of PNS. PNS is more common in LC patients and its frequency is higher in SCLC than in other types of LC.

PNS may involve almost all systems and may appear before or after the diagnosis of cancer. The diagnosis of the lesions that appear before LC diagnosis can significantly affect the outcomes by allowing the early identification of LC and changing its prognosis through timely treatment. Similarly, recurrences and remissions of PNS provide important clues during cancer follow-up.

A clear understanding of the mechanisms leading to PNS development in LC patients and improvements in the diagnostic and treatment methods will significantly provide positive improvements in the cancer treatment.

Author details

Dilaver Tas

Address all correspondence to: dilavertas@gmail.com

Istanbul Research and Training Hospital, Baskent University, Istanbul, Turkey

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